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Parent-of-Origin Effect in Transmission of Bipolar Disorder

Tadafumi Kato, George Winokur, William Coryell, Martin B. Keller, Jean Endicott, and John Rice

Department of Psychiatry, University of Iowa College of Medicine, Iowa City, Iowa (T.K., G.W., W.C.); Butler Hospital/Brown University, Providence, Rhode Island (M.B.K.); New York State Psychiatric Institute, New York, New York (J.E.); Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri (J.R.)

Recently, possible involvement of a parent-of-origin effect in the transmission of bipolar disorder has been suggested. We examined the possible contribution of parent-of-origin effect by using data from a large family and family history study of bipolar patients in the Collaborative Depression Study. In 276 probands with bipolar I disorder, family histories were examined using three diagnostic criteria: 1) bipolar I disorder, 2) bipolar I or bipolar II disorder, and 3) bipolar disorders or recurrent unipolar depression for parents and siblings. An excess of affected mothers was not observed when unipolar depression was excluded. Age-at-onset was significantly lower in probands having a father with bipolar disorders or recurrent unipolar depression than in probands with an affected mother. This difference was not observed when unipolar depression was excluded. There was no significant difference of prevalence rate in children of affected mothers and those with affected fathers. These data do not support the contribution of parent-of-origin effect in the transmission of bipolar disorder.

KEY WORDS: genomic imprinting, maternal transmission, mitochondrial inheritance, manic depressive illness, affective disorder

INTRODUCTION

A gender difference in patterns of inheritance of bipolar disorder has been noted: mothers of probands have higher prevalence rate than fathers [Helzer and Winokur, 1974], male-to-male transmission is rare in bipolar disorder [Reich et al., 1969], and maternal relatives have higher prevalence rate of affective disorders than paternal relatives [Winokur and Reich, 1970].

Recently, modes of inheritance which account for such gender-difference of transmission, without following Mendel's laws, have drawn attention in psychiatric genetics [Gelernter, 1995]. They are referred to as "parent-of-origin effect," meaning that the gender of a transmitting parent affects the expression of illness in offspring [Hall, 1995]. Mitochondrial inheritance [Giles et al., 1980], genomic imprinting [Hall, 1990], and triplet repeat expansion [La Spada et al., 1994] have been implicated in the transmission of bipolar disorder.

Mitochondrial DNA (mtDNA) is contained not in the nucleus but in the mitochondrion in multiple copies. Because mitochondria are few in sperm but many in oocytes, mtDNA is transmitted mainly from mother to children [Giles et al., 1980]. Therefore, all children (males and females) of an affected mother are at risk in mitochondrial inheritance. Although actual patterns of transmission are not always simple, this is a hallmark of maternal inheritance. Two families in which mitochondrial myopathy with multiple mtDNA deletions was cosegregated with recurrent depression were reported [Ciafaloni et al., 1991; Suomalainen et al., 1992]. There are case reports in which a patient with an mtDNA mutation had affective disorders [Shanske et al., 1993; Stewart and Naylor, 1990; Sweeney et al., 1993; Wallace, 1970; Kato and Takahashi, 1996]. These findings suggest that aberrant mtDNA may relate to pathophysiology of affective disorders.

In genomic imprinting, expression of a gene depends on whether that gene has a paternal or maternal origin [Hall, 1990]. When the gene is paternally imprinted, only the gene from the mother is expressed. In this case, only the mother can transmit the disease. Inactivation of a gene may be accomplished by methylation of DNA. This mechanism has also been implicated in bipolar disorder [Flint, 1992]. Recently, Stine et al. [1995] have reported that excess sharing of the paternally, but not maternally, transmitted alleles was observed at markers on chromosome 18. This finding may

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Address reprint requests to Tadafumi Kato, M.D., now at the Department of Psychiatry, Shiga University of Medical Science, Seta-tsukinowa-cho, Otsu, Shiga 520-21, Japan.

suggest that a maternally imprinted locus in this region is responsible for bipolar disorder.

Triplet repeat expansion was first reported in fragile X syndrome. This unstable trinucleotide repeat increases generation to generation. Because the length of this repeat relates to earlier age-at-onset and more severity, each subsequent generation has lower age-at-onset. This phenomenon, called "anticipation," was reported to be present in bipolar disorder [Asherson and Owen, 1994; McInnis et al., 1993; Nylander et al., 1994]. It has already been reported that the CAG repeat was expanded in bipolar disorder [O'Donovan et al., 1995]. Because the extent of this expansion from generation to generation depends partly on the gender of the transmitting parent [La Spada et al., 1994], age-at-onset of a proband relates to the gender of the transmitting parent in diseases caused by triplet repeat.

Recently, two groups have reported clinical genetic studies suggesting the contribution of parent-of-origin effect in the transmission of bipolar I disorder. McMahon et al. [1995] have proposed that maternal transmission, i.e., mitochondrial inheritance or genomic imprinting, may be involved in the transmission of bipolar disorder, reporting that mothers as compared to fathers, and maternal relatives as compared to paternal relatives, had higher prevalence rates of affective disorders in 31 pedigrees of bipolar disorder. Grigoroiu-Serbanescu [1992] and Grigoroiu-Serbanescu et al. [1995] have also suggested that genomic imprinting may be involved in transmission of bipolar disorder, reporting that probands with an affected father had significantly earlier age-at-onset.

In our study, the large data base in the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression was analyzed to examine possible contribution of parent-of-origin effect in the transmission of bipolar disorder.

The following strategies listed below were used to examine possible involvement of parent-of-origin effect in the transmission of bipolar disorder: 1) whether or not probands having an affected mother were more frequently seen than probands having an affected father; 2) whether or not probands with an affected mother had more affected siblings than probands with an affected father; and 3) comparison of age-at-onset between probands with an affected mother and those with an affected father.

These comparisons were made using three types of diagnostic criteria: 1) bipolar I disorder, 2) bipolar I disorder or bipolar II disorder, and 3) bipolar disorders or recurrent unipolar depression.

SUBJECTS AND METHODS

Two hundred and seventy-six probands (148 women and 128 men, mean age 36.5 (SD, 13.1) years) who had bipolar I disorder were selected from the data base of the NIMH Collaborative Program on the Psychobiology of Depression. Bipolar I disorder includes schizoaffective mania and manic disorder, according to Research Diagnostic Criteria (RDC) [Spitzer et al., 1978]. All probands were interviewed using the Schedule for Affective Disorder and Schizophrenia (SADS) [Endicott and Spitzer, 1978]. Age-at-onset of probands was defined as age of first major affective episode. Family history was obtained from the proband and all available informants. All relatives including parents, siblings, spouse, and children were diagnosed by family history RDC (FH-RDC) [Spitzer et al., 1978]. For 65% of probands, all available relatives were interviewed by blind raters using the Schedule for Affective Disorder and Schizophrenia, Lifetime Version (SADS-L) [Endicott and Spitzer, 1978] and diagnosed by RDC. In this paper, family diagnoses were based both on family history and family study after all information was collected. Details of this research project have been reported elsewhere [Andreasen et al., 1987].

Of 276 mothers of the probands, 140 were interviewed, while only 89 of 276 fathers were interviewed. Ages of parents were not significantly different between mothers (mean, 61.1 (SD, 11.8) years) and fathers (mean, 60.3 (SD, 12.6) years).

The affected status of parents and siblings was classified into three diagnostic groups as follows: 1) bipolar I disorder, 2) bipolar disorders, and 3) bipolar disorders or recurrent unipolar depression. The first category contains bipolar I disorder, schizoaffective mania, and manic disorder. The second category includes the three diagnoses in the category 1 and bipolar II disorder. The third category includes all diagnoses in category 2, and recurrent unipolar depression. These disorders, other than those in category 1, were regarded as "alcoholism" and excluded from calculation if they were accompanied by alcoholism whose age-of-onset is the same as or before the age-of-onset of affective disorders.

For statistical analysis, the χ^2 test, Fisher's exact probability test, and Student's t-test were used.

RESULTS

Sex Distribution of Affected Parents

At first, 276 probands were classified into three groups by the affected status of their parents: unilineal, bilineal, or neither parent affected. Among the unilineal probands, two groups were compared with each other: in group 1, only the mother was affected (maternal); in group 2, only the father was affected (paternal) (Table I). Whether or not the observed frequency of probands in groups 1 and 2 deviated from the expected 1:1 ratio was examined by χ^2 test for goodness of fit.

When diagnosis criteria 1 or 2 (bipolar I disorder, or bipolar disorders) were used for the parents, there was no significant deviation of number of probands maternally or paternally affected. When diagnostic criteria 3 (bipolar disorders or recurrent unipolar depression) were used for the parents, there were significantly more maternally-affected probands than paternally-affected probands. This significant difference was not seen in male probands, but only in female probands.

Age-at-Onset of Probands

Age-at-onset was compared between probands with an affected mother and those with an affected father (Table II). Probands having a father with bipolar disorders or recurrent unipolar depression (criteria 3) had significantly lower age-at-onset than those with an af-

TABLE I. Comparison Between Maternal vs. Paternal Transmission

Diagnosis of parents		Unilineal		Bilineal	Neither affected
		Maternal	Paternal		
Bipolar I disorder	Total (female, male)	12 (7, 5)	16 (5, 11)	1 (0, 1)	247 (136, 111)
Bipolar I disorder or bipolar II disorder	Total (female, male)	15 (9, 6)	18 (6, 12)	2 (0, 2)	241 (133, 108)
Bipolar disorders or recurrent unipolar	Total (female, male)	41 (25, 16)	22 (9, 13)*	9 (2, 7)	204 (112, 92)

*Maternal vs. paternal, $P < 0.02$ ($\chi^2 = 5.7$).

fected mother. No significant difference of age-at-onset was found between these two groups when diagnostic criteria 1 and 2 (bipolar I disorder or bipolar disorders) were used.

Prevalence Rate in Siblings

Prevalence rate in siblings of probands with an affected mother (group 1) was compared with that in siblings of probands with an affected father (group 2), using the χ^2 test for independence (Table III). When there was a cell whose frequency was <5, Fisher's exact probability test was used. There was no significant difference in age and number of interviewed subjects between group 1 and group 2, regardless of diagnostic criteria used.

There was no significant difference of prevalence rate between group 1 and group 2, regardless of diagnostic criteria of the parents and siblings.

DISCUSSION

The present finding, that probands with a mother with bipolar disorders or recurrent unipolar depression were more frequently seen than paternally-affected probands, is compatible with many previous reports [Reich et al., 1969; Winokur and Reich, 1970; Taylor and Abrams, 1973; Helzer and Winokur, 1974], as well as that by McMahon et al. 1995]. This significant difference, however, was not observed when bipolar I disorder or bipolar disorders were regarded as a phenotype. It is well-known that the prevalence rate of unipolar depression in females is twice that in males, either in relatives of bipolar probands or in the general population [Weissman and Klerman, 1977]. Therefore, the finding that the affected mother is more frequently seen than the affected father may not be related to a parent-of-origin effect but to a higher prevalence rate of unipolar depression in females.

Although unipolar depression is more frequently seen in relatives of bipolar probands, the prevalence rate of unipolar depression in relatives of bipolar probands was only twice that in the general population. Therefore, even if some unipolar depressives in relatives of bipolar probands are the expression of the gene responsible for bipolar disorder, half of them could derive from the normal expectation seen in the population [Winokur, 1994]. In the analysis using diagnostic criteria 3 (bipolar disorders or recurrent unipolar depression), 26 of 41 mothers had unipolar depression, while only 8 of 22 fathers had unipolar depression. If we assume that half the parents with unipolar recurrent depression had the genetically bipolar disorder in this data set, there was no significant difference between maternal vs. paternal transmission (28:18, [41–26/2] : [22–8/2]). However, it should be noted that the observed excess of mothers having unipolar depression in this analysis, 26:8, is higher than the expected ratio of 2:1.

We could not examine the finding that affective disorder is more frequently seen in maternal relatives than in paternal relatives [Winokur and Reich, 1970; McMahon et al., 1995], because family histories of siblings of parents were not examined in this study. However, since the core feature of maternal inheritance, that affected mothers are more frequently seen than affected fathers, was not observed in this study, significant contribution of maternal inheritance in the transmission of bipolar I disorder is unlikely, even though we could not examine maternal and paternal relatives.

Previous studies in which only bipolar disorder was regarded as a phenotype have also shown no gender-difference in transmission. Those studies have suggested that the mode of inheritance of bipolar disorder might be an autosomal-dominant and multifactorial inheritance [Smeraldi et al., 1981; Weissman et al., 1984; Rice et al., 1987].

TABLE II. Age-at-Onset of Probands vs. Disease in Parents

Diagnosis of parents	Unilineal (mean (SD) years)		Bilineal (mean (SD) years)	Neither affected (mean (SD) years)
	Maternal	Paternal		
Bipolar I disorder	21.2 (8.7) (N = 12)	21.3 (7.7) (N = 16)	18 (N = 1)	25.3 (10.5) (N = 247)
Bipolar I disorder or bipolar II disorder	21.3 (8.6) (N = 15)	20.8 (7.4) (N = 18)	13.0 (7.0) (N = 2)	25.5 (10.5) (N = 241)
Bipolar disorders or recurrent unipolar	24.5 (8.7) (N = 41)	21.0 (4.2) (N = 22)*	19.0 (11.9) (N = 9)	25.6 (10.8) (N = 204)

*Maternal vs. paternal, $P < 0.05$ ($t = 2.15$).

TABLE III. Prevalence in Siblings in Relation to Diagnoses of Parents*

Diagnosis of parents	Diagnosis of siblings	Sister		Brother		Total	
		Maternal	Paternal	Maternal	Paternal	Maternal	Paternal
Bipolar I disorder	BP I	5%	11%	17%	8%	9%	10%
	BPs	10%	22%	25%	20%	16%	21%
	BP/RD	30%	28%	25%	20%	28%	25%
	N	20	36	12	25	32	61
Bipolar I disorder or bipolar II disorder	BP I	5%	11%	13%	7%	8%	9%
	BPs	9%	22%	19%	17%	13%	20%
	BP/RD	32%	28%	31%	21%	32%	25%
	N	22	36	16	29	38	65
Bipolar disorders or recurrent unipolar	BP I	4%	8%	5%	6%	4%	7%
	BPs	11%	15%	9%	10%	10%	13%
	BP/RD	23%	23%	14%	13%	18%	18%
	N	57	40	57	31	114	71

*BP I, bipolar I disorder; BPs, bipolar I disorder or bipolar II disorder; BP/RD, bipolar disorders or recurrent unipolar depression.

As noted, Grigoroiu-Serbanescu [1992] and Grigoroiu-Serbanescu et al. [1995] have suggested that genomic imprinting may be related to bipolar illness, based on a finding that probands with an affected father had a significantly younger age-at-onset. Although this finding was confirmed in this study (Table II), it disappeared when only bipolar disorder was regarded as an affected phenotype for parents. When "bipolar disorder or recurrent unipolar depression" was used as a phenotype definition for parents, most affected mothers had unipolar depression (26/44), while fewer affected fathers had unipolar depression (8/22). This difference may have caused an apparent difference of age-at-onset between probands with an affected mother and those with an affected father, based on the assumption that probands having a parent with bipolar disorder have lower age-at-onset than those having a parent with unipolar depression. This may be partly true, at least in this sample. In unilineal families, probands having a parent with bipolar I disorder tended to have lower age-at-onset (21.1 ± 6.9 years, n = 19 years) than probands having a parent with recurrent unipolar depression (24.6 ± 8.6 years, n = 34 years, $P = 0.10$). Therefore, this finding of lower age-at-onset in paternal transmission may also be caused by inclusion of unipolar depression in affected phenotypes.

Data on the prevalence rate of bipolar disorder in siblings of probands, i.e., that there is no difference of prevalence rates between maternally affected siblings and paternally affected siblings, do not favor the involvement of mitochondrial inheritance in bipolar disorder. This is compatible with the finding by Grigoroiu-Serbanescu et al. [1995] that there was no significant difference of prevalence rate in first- or second-degree relatives of probands with an affected mother and those of probands with an affected father.

Although these data were collected from hospitalized patients or newly-evaluated patients from outpatient clinics without any exclusion criteria such as exclusion of bilineal pedigrees, they still cannot be free from all ascertainment or observation biases. Because the number of interviewed subjects was significantly different between mothers and fathers, this may have affected the diagnosis of parents. Although we did not use lifetime morbid-risk analysis, this does not affect the results because the mean age was similar between the two groups compared.

It cannot be completely ruled out that lack of significant gender difference in parents having bipolar disorder might be a type II error due to decrease in sample size. When the expected ratio of affected mothers is 0.50 and the increased ratio of affected mothers is 0.67, the statistical power to detect significant difference in 28 samples is 55%.

It should be noted that this study does not exclude a possible pathophysiological significance of mtDNA in bipolar disorder. In the family of familial mitochondrial myopathy with multiple deletions of mtDNA in which expression of depression was noted, the disease was not maternally transmitted but inherited in an autosomal-dominant manner [Suomalainen et al., 1992]. Recently, this autosomal locus predisposing to deletions of mt DNA was assigned to 10q 23.3–24.3 [Suomalainen et al., 1995]. There may be other nuclear genes which interact with mtDNA. In addition, 2 bipolar patients who had deleted mtDNA in the study of Kato and Takahashi [1996] did not have an affected mother. In this case, somatic mutation of mtDNA, which is usually also observed in mitochondrial myopathies [DiMauro and Moraes, 1993], may have had a pathophysiological role.

In conclusion, this report does not support previous findings suggesting involvement of parent-of-origin effect in bipolar disorder, in that affected mothers were not more frequently seen than affected fathers, and probands with an affected father did not have lower age-at-onset when recurrent unipolar depression was excluded from the affected phenotype.

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